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WAR MEDICINE AND SURGERY

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THE PRESENT POSITION OF THE VITAMINS.[1]

Definition and Classification of Vitamins.

VITAMINS have the following characteristics: (*a*) they are organic compounds which are required for the maintenance of life and for normal growth; (*b*) they must be provided in foods, since they cannot usually be synthesized by the organism requiring them; (*c*) they are effective in very small amounts; (*d*) they do not furnish energy and are not employed as building units in the structure of the organism, but they are essential for the transformation of energy and for the regulation of metabolism.

At least thirteen different groups of substances, all of which have been synthesized, are now recognized as vitamins: (*a*) vitamin *A*; (*b*) eight components of the vitamin *B* complex, namely, thiamin (vitamin B_1 or aneurin), riboflavin (vitamin B_2), pyridoxin (vitamin B_6), niacin (nicotinic acid), pantothenic acid, biotin, inositol, and *p*-aminobenzoic acid; (*c*) ascorbic acid (vitamin *C*); (*d*) the *D* group of vitamins; (*e*) the *E* group of vitamins; and (*f*) the *K* group of vitamins. Several other substances have been claimed as vitamins, but it is not certain that they will be finally accepted as such.

Vitamin *D* can be produced in the skin by exposure to ultra-violet rays, but with this single exception, probably all the vitamins in the above list must be provided for man in his food. This is not the case with all animals; for example, as far as we know, only man, higher apes and guinea-pigs require ascorbic acid in the food; other animals can synthesize it themselves.

Absorption of Vitamins.

In a properly functioning organism all the vitamins are readily absorbed from the intestinal tract. The fat-soluble vitamins, especially *A* and *K*, require bile salts for their absorption, so that when these bile salts are absent, as in blockage of the common bile duct, absorption is very deficient even if there is an abundance of vitamins in the food.

The Study of the Normal Functions of Vitamins.

The use of different vitamins by the body can be studied from two points of view. The first is the effect of deficiency of any of the vitamins in producing pathological conditions, either in special tissues or in the body as a whole. The second, and the more fundamental, is the use of vitamins for the normal processes of various tissues. In some respects the former approach is the more interesting to the medical practitioner, but the changes resulting from deficiency of vitamins cannot be properly understood without some knowledge of the functions of vitamins in normal metabolism.

[1] This article was originally given in a course of lectures arranged by the New South Wales Post-Graduate Committee in Medicine. The lecturer was Professor H. Priestley, who has kindly consented to the publication of his address as one of the series of articles on war medicine and surgery.

In regard to some vitamins we know very little of their function in normal cells; in regard to others our knowledge is reasonably clear, as is shown by the following account of the role of certain water-soluble vitamins in tissue oxidations.

The breakdown of carbohydrates, fats and amino acids in the body, with the liberation of energy, is brought about, in the main, by a series of oxidation reactions. In these reactions certain of the vitamins play a fundamental part. Nicotinic acid, or rather its amide, is a part of the molecule of each of the coenzymes which act in conjunction with a large series of specific proteins, and bring about oxidation of the metabolite. Although this action is a form of oxidation, it must be understood that there are several further stages in the series before oxygen itself comes into the picture. The next step between the substrate and oxygen is provided by riboflavin in various combinations with proteins. Then follow a series of other substances not directly related to vitamins, and finally molecular oxygen. If any part of this chain is broken cellular oxidation is either prevented or impaired; hence the importance of nicotinic acid and riboflavin.

Riboflavin is also a part of other enzyme systems such as amino acid oxidase and xanthine oxidase. Thiamin, combined with phosphoric acid to form a substance called co-carboxylase, is essential for the formation of enzyme systems concerned with the breakdown of keto-acids, which occur in the late stages of carbohydrate and fat metabolism. The effect of thiamin deficiency is to cause accumulation in the body of certain keto-acids, particularly pyruvic acid; and the pathological results of thiamin deprivation are due either to this accumulation, or to the breakdown in metabolism which it signifies.

Certain of the other water soluble vitamins, particularly pyridoxine, pantothenic acid and *p*-aminobenzoic acid, probably have functions similar to the above, but, as yet, the picture is not so clear.

Individual Vitamins.

The individual vitamins will now be discussed in turn.

Vitamin A.

Vitamin *A* is present as such only in foods of animal origin. In plant materials and, to some extent, in animal foods as well, it is present as one or other of the provitamins—the carotenes—which are converted in the animal body to vitamin *A*. Carotene is not nearly as well absorbed from the gut as vitamin *A*, though the carotene of green vegetables is, in general, much more readily absorbed than that in carrots. Carotene, like vitamin *A*, requires bile salts for proper absorption.

There is no certainty yet as to how vitamin *A* acts in the body, but a consideration of the pathological effects of deficiency of this vitamin throws some light on the problem. Proliferating epithelial structures are affected in a way which suggests that vitamin *A* is necessary for some chemical process uniquely related to the normal differentiation of epithelial cells. The sequence of events when deficiency occurs is as follows: firstly, there is

atrophy of the epithelium, and then proliferation of basal cells, and differentiation of the new cells into a stratified keratinizing epithelium. This replacement epithelium is identical in all the affected areas regardless of the original structure and function of the region concerned. The characteristic metaplasia is seen in the salivary glands, the mouth, the respiratory tract as far as the bronchi, the genito-urinary tract, the epithelial portions of the eye, and the surface epithelium; epithelia which do not undergo these changes are the mucosa of the stomach and intestines and the epithelium of the renal tubules.

When this metaplasia occurs it produces a reduction in the resistance of the epithelium to invasion by bacteria. If vitamin *A* is administered, there is a rapid return of the epithelia to their normal structure, and resistance to bacteria is restored to normal. It is in this sense only that vitamin *A* is anti-infective. It has been claimed that large doses of the vitamin increase the resistance to respiratory infections, but careful investigations, controlled statistically, show that this is not correct.

The enamel organ of the teeth is an epithelial structure and, during deficiency of vitamin *A*, undergoes changes similar to those of other epithelia. Consequently such deficiency interferes with the production of enamel in growing teeth and, secondary to this, there is a failure in the formation of dentine. Thus the supply of vitamin *A* is important in late fœtal life and early infancy when the teeth are undergoing their most rapid development.

Vitamin *A* has another specific effect. It helps to form visual purple in the retina, and since this pigment is necessary for vision in dim light, the first symptom of vitamin *A* deficiency is usually either night blindness or, at any rate, reduced ability to see in dim light. Not all night-blindness, however, is due to deficiency of vitamin *A*.

Vitamin *A* deficiency retards the growth of bones and, in particular, it interferes with endochondral bone formation. One result of this is that the growth of the spinal cord outstrips the growth of the spinal column, and various lesions are caused by pressure effects on the nervous tissue.

It can be said by way of summary, then, that vitamin *A* acts essentially as a stimulus to the growth and differentiation of cells, particularly epithelial cells.

Thiamin.

It has already been mentioned that thiamin is essential for the later stages in the oxidation of carbohydrates in the body, and, more specifically, for the utilization of pyruvic acid. In deficiency of thiamin, pyruvic acid accumulates in the tissues and can easily be detected. In acute deficiency there is no permanent pathological change in the tissues, provided the vitamin is given before the animal becomes moribund, but, in chronic insufficiency, permanent degenerations occur in the central and peripheral nervous systems. It is significant that the cells of the nervous tissue are totally and uniquely dependent upon oxidation of carbohydrate for their function and integrity. Whether the changes in the nervous system and the heart are due to the accumulation of pyruvic acid and allied substances, or to carbohydrate starvation of the cells, is not certain, but the latter hypothesis seems more likely. As might be expected, thiamin requirements are proportional to the amount of carbohydrate used by the cells. As well as being necessary for the full oxidation of carbohydrate and fat, thiamin is needed for the synthesis of fat from carbohydrate.

Chronic alcoholism frequently leads to thiamin deficiency. It is not certain whether this is due to excessive destruction of thiamin in the combustion of alcohol—a rather improbable hypothesis—or to some specific toxic effect of alcohol on cells, or to the fact that the subject does not get enough food containing thiamin since the greater part of the diet is spirits and the appetite for other foods is impaired. Toxic substances such as lead, nicotine and arsenic can also bring about a state of acute thiamin deficiency. In all these cases the administration of thiamin is very helpful.

Partial deficiency of thiamin has been produced experimentally, and the subjects have shown mental and physical inefficiency, irritability, depression, headache, backache, anorexia, nausea, epigastric discomfort after meals and constipation. These symptoms are rather vague and not uncommon, but they should lead the doctor to investigate the diet and possibly to give thiamin preparations for a time. It is obviously useless to give thiamin to any patient who is already receiving sufficient in his diet. If the diet has for some reason been severely restricted, thiamin may well be necessary, but there will be other dietary deficiencies that are at least as important.

It has been shown that a partial thiamin deficiency is not uncommon in breast-fed infants in Australia.[9] The symptoms are: failure to gain weight at the normal rate, constipation and vomiting. Administration of thiamin to either mother or child cures the condition, so that there must be several Australian mothers who have a diet deficient in thiamin.

The relation of thiamin to gastro-intestinal dysfunction in general must at present be considered as presumptive only; published reports on this problem are contradictory.

Riboflavin.

Riboflavin is like thiamin in being necessary for certain metabolic processes in cells, but it covers a much wider range of metabolites than does thiamin. Thus it is necessary for the oxidation of coenzymes I and II and so is connected with the oxidation of a large number of carbohydrate derivatives. It is also part of the enzyme system which oxidizes xanthine to uric acid and is a constituent of other enzyme systems. It is difficult to connect these facts with the results of insufficiency of riboflavin. A common result of ariboflavinosis in animals is sudden death. There are no apparent morphological changes to account for such deaths, but a possible explanation is that cellular asphyxia has resulted from the breakdown of cellular oxidation.

In man an early sign of deficiency of riboflavin is an ingrowth of capillaries into the cornea. This is probably a response to failing cellular metabolism in the cornea. It is not easy to explain the other symptoms and signs such as ocular disturbances, seborrhœic desquamation around the mouth and ears, and a typical glossitis, which causes the tongue to assume a magenta colour. Most of the obvious signs in man are related to the region of the mouth and eyes, but there is, as well, a disturbance of cellular metabolism throughout the body, and the sudden death which sometimes occurs in malnutrition may be an indication of this. Ariboflavinosis is probably uncommon in Australia in normal times, but a number of cases have occurred recently. The condition reacts quickly and favourably to the administration of riboflavin.

It is a matter of interest that penicillin B, which it is claimed, will kill staphylococci *in vitro* in a dilution of 1 in 2,000,000,000, is a riboflavin compound. It acts as an enzyme splitting glucose to gluconic acid and hydrogen peroxide, the latter being the toxic agent. This mode of action explains why penicillin is so little toxic for man, because any hydrogen peroxide formed in his body cells would be rapidly destroyed by catalase. For the same reason larger doses of penicillin are required *in vivo* than *in vitro*.

Pyridoxin.

Pyridoxin, one of the most recently discovered vitamins, is probably connected with oxidation systems in the cells, but there is, as yet, no conclusive evidence for this statement. In rats pyridoxin deficiency causes a symmetrical dermatitis, while in dogs microcytic anæmia results. Deficiency in man probably occurs only in a multiple avitaminosis such as exists in pellagra. Nervousness, muscular cramps, rigidity, and similar symptoms in pellagrins have been greatly improved by giving pyridoxin. It has also been claimed that pyridoxin is useful in *paralysis agitans*, but this is doubtful.

Niacin.

Niacin is an essential component of coenzymes I and II, which are partly responsible for the oxidation of carbohydrates in the body. It is probably also linked with the metabolism of water in the body, for deficiency leads to

the retention of water. Another effect of deficiency is a breakdown of hæmoglobin to other porphyrins, which circulate in the blood stream and may be responsible for the sensitivity to light which is characteristic of pellagra.

Although pellagra is due to a multiple deficiency of vitamins, the main symptoms are probably caused by lack of niacin. This is not quite certain, for uncomplicated deficiency of niacin probably does not occur in man, so that one cannot be sure which of the symptoms and signs found in pellagra are due to insufficiency of niacin.

Administration of niacin by mouth is often followed by flushing, burning and itching of the skin. These symptoms are not produced by niacin amide, and since this derivative is active therapeutically, it is the preparation recommended for clinical use.

Pantothenic Acid.

It is not known what symptoms, if any, are produced in man by deficiency of pantothenic acid, so that, at present, there are no indications for its clinical use. However, all animals so far investigated require pantothenic acid, so that man, too, probably needs it. The blood level has been found to be low in pellagra and beriberi.

Other Constituents of the Vitamin B Complex.

Nothing is known about the requirements by man for inositol and *p*-aminobenzoic acid. Biotin, the latest of the vitamins to be synthesized, is necessary for man, but only in extremely small amounts; and as it is very widespread in foodstuffs, lack of it probably does not ever occur. Experimentally, deficiency of biotin has been produced in man by the administration of large amounts of dried egg-white. Uncooked egg-white contains a protein which forms a complex with biotin and so renders the latter unavailable to the body. The giving of raw egg-white to patients on a low diet would therefore seem to be unwise.

One of the symptoms of biotin deficiency in man is a fine branny desquamation of the skin, and it has been claimed that good results have been obtained by the administration of biotin in seborrhœic dermatitis and psoriasis. The known variability of these conditions, however, makes judgement of the problem difficult.

Ascorbic Acid.

Vitamin *C* or ascorbic acid has well-defined actions in the body, and these explain the effects of deficiency. It is necessary for those cells which form extracellular glucoproteins such as are found in connective tissue, bone, dentine and intercellular cement. Ascorbic acid has the capacity for reversible oxidation and reduction and it probably plays an essential part in the enzyme systems of those cells which produce collagen and collagen-like substances. It is also an important constituent of other cell enzyme systems, particularly those concerned in the oxidation of carbohydrates and amino acids.

The effects of deficiency are practically confined to supporting tissues, where there is a failure in the formation and maintenance of intercellular materials. All the symptoms of scurvy can be explained on the basis of insufficiency of matrix substances. The slow healing of wounds in scorbutic or even prescorbutic conditions can be explained in the same way, since the formation of new capillaries and the deposition of collagen are prevented.

Ascorbic acid is also concerned in detoxicating mechanisms, and is required in larger amounts when toxic substances are present; for example, during bacterial infections. In the feeding of patients who have fevers care should be taken either to supply a diet containing ample ascorbic acid or, if necessary, to give the synthetic vitamin. There is considerable evidence that partial deficiency of ascorbic acid leads to a lowered resistance towards infection.

Increased ascorbic acid is necessary for pregnant women, to enable proper formation of the matrix of teeth and bone in the fœtus. The need for ascorbic acid in young infants does not require stressing. The great value of germinated peas as a rich source of ascorbic acid is not sufficiently well known. The maximum content is present on the fourth day of germination; the peas, lightly cooked, are very palatable.

A partial deficiency of ascorbic acid is the commonest vitamin deficiency found in Australia.

Vitamin D.

There are several closely related chemical substances with vitamin *D* activity, but only two of these are of importance for man. These two are vitamin D_3, which is obtained by the irradiation of 7-dehydrocholesterol, and vitamin D_2 or calciferol obtained by the irradiation of ergosterol. D_3 is the principal *D* vitamin in fish liver oils and is the one produced by irradiation of the skin. D_2 and D_3 seem to be equally efficacious for man; in the case of chickens, D_2 shows little activity, whereas D_3 is very effective. Vitamin *D* is found in various fish liver oils, but the amount present is variable. Thus some tuna liver oils contain four hundred times as much vitamin *D* as an average cod liver oil.

The exact mode of action of vitamin *D* is not known. It is essential for the proper absorption, retention and metabolism of calcium and phosphorus, but there is no agreement as to which of these three processes is most affected by it. In vitamin *D* deficiency there is a great increase in the phosphatase content of the blood, and the level may fall slowly even after the administration of vitamin *D*. This has not been adequately explained. An early sign of deficiency is a lowered phosphorus content of the blood, and this may or may not be followed by a lowering of the calcium content. At the same time there is a lessened retention of calcium and phosphorus in the body, and these elements are either deposited in the bones in decreased amounts, or not deposited at all, or even withdrawn from the bones. It seems reasonably certain that, in man, at any rate, vitamin *D* is necessary for bone growth quite apart from its effect on the absorption of calcium and phosphorus.

Rickets is not only a disease of bone, for all the tissues are involved to some extent. The muscles are particularly affected, but this is not surprising when one considers the important part played by calcium and phosphorus in cellular metabolism.

It has been shown that if the diet of a woman during pregnancy is inadequate in respect of vitamin *D*, calcium and phosphorus, then the baby she bears may develop demonstrable rhachitic signs in the first year of post-natal life, even though the child's diet contains an abundance of antirhachitic factors.[1] It seems that a child is unable to absorb sufficient minerals from the intestinal tract to cope with the huge requirements of the early period of active growth, and he is therefore liable to develop rickets unless he has been born with an adequate store of minerals in his bones. Pregnant women consequently require more vitamin *D* than other adults, and, in some cases where the diet does not provide sufficient, they should be given an extra supply in the form of a vitamin preparation. It is very doubtful, however, whether other adults in this country will derive any benefit from the administration of vitamin *D*, and it is difficult to understand why vitamin *D* is so widely prescribed.

Vitamin E.

There are at least three substances in natural products with vitamin *E* activity, but α tocopherol is the most active. These substances are of very widespread occurrence in vegetable foods, but poor in animal foods. Deficiency of vitamin *E* must be very uncommon in man, if it occurs at all. The primary action of the vitamin seems to be directed to certain activities of cell nuclei. The pathological changes resulting from its deficiency in animals are: failure of early embryonic development, irreparable degeneration of male germinal epithelium, dystrophy of skeletal muscles and encephalomalacia. The evidence for its usefulness in man is based on clinical reports, mostly poorly controlled, of its value in habitual and threatened abortion, in various types of muscular dystrophy and in certain neuromuscular syndromes.

Creatine excretion in the urine increases considerably in vitamin *E* deficiency, but many other factors increase the creatine output, so that estimations of its level are not of much value in deciding whether the vitamin is being given in adequate amounts. The value of vitamin *E* administration in man must for the present be regarded as not proven.

Vitamin K.

Two natural products with vitamin *K* activity are known. They have the same napthoquinone nucleus, 2-methyl-1, 4-napthoquinone. It is of great interest, and, from a clinical point of view of great importance, that this nucleus is more active than the natural products.

Vitamin *K* is taken in food, but is also formed in the intestinal tract by the action of bacteria. Bile salts are necessary for the absorption of the natural products and for the above-mentioned substitute, so that when bile is prevented from reaching the intestine, absorption of vitamin *K* does not take place and deficiency may occur in the presence of plenty. However, a number of water-soluble esters of napthoquinone have been made and these can be absorbed in the absence of bile salts. In obstructive jaundice the results are quite satisfactory when one of these water-soluble derivatives is given orally.

Vitamin *K* is necessary for the production of prothrombin by the liver, so that the symptoms of its deficiency are those of reduced prothrombin in the blood; clotting of the blood is delayed and hæmorrhages occur in various parts. The exact explanation of the bleeding is not yet known and vitamin *K* is certainly not a panacea for hæmorrhages. It is of use only when the hæmorrhages are associated with reduced prothrombin levels, and practically the only conditions where it is of value clinically are: (*a*) obstructive jaundice; (*b*) intestinal disorders such as sprue and ulcerative colitis, which lead to poor absorption of vitamin *K*; and (*c*) hæmorrhagic disease of the newborn. It is useless in hæmophilia; and it is of little value in non-obstructive jaundice with considerable liver damage, since the low blood prothrombin in this case is not due to deficiency of vitamin *K*, but to inability of the damaged liver cells to manufacture prothrombin.

Vitamin P.

Vitamin *P* is one of the doubtful vitamins. Lack of it is said to lead to capillary fragility, and a number of workers believe that it is necessary for some animals, including man. On the other hand, scurvy has been cured by the administration of ascorbic acid alone, so that the position of this substance as a vitamin must be held in doubt.

Proprietary Preparations of Vitamins.

The best source of all the vitamins that man needs is still natural food. If there is a deficiency of any vitamin there is almost certainly a deficiency in other food constituents as well, and the administration of a single vitamin in the form of tablets or extracts will not make good the full deficiency. On the other hand, there are certain special cases in which pharmaceutical preparations of individual vitamins are very useful. This is particularly so when the condition of deficiency is acute and when the diet for some reason or other cannot be satisfactorily adjusted. There can seldom be any justification, however, for giving polyvitamin preparations.

Summary of the Important Sources of the Various Vitamins.

The important sources of the vitamins may be listed as follows:

Vitamin A: (*a*) Animal fats, particularly the fish liver oils, but also from the liver oils of sheep and oxen; butter; egg yolk; and milk. Of the fish liver oils, halibut, tuna and the Australian snapper shark each have a higher content of vitamin *A* than cod liver oil. (*b*) Various yellow fruits and vegetables such as carrots, yellow maize, bananas and apricots are sources of carotene. (*c*) Greenstuffs are all sources of carotene.

Thiamin: Yeast and autolysed yeast products, pork, peanuts, oatmeal, wholemeal, liver and peas. White flour has a reduced content of thiamin compared with wholemeal flour, but the problem of obtaining adequate thiamin from bread is not nearly as difficult here as in England and America. Some types, at least, of Australian white flour have retained large quantities of the vitamins of the wheat berry.

Riboflavin: Yeast, liver, milk, eggs, kidney, beef, peanuts and leafy vegetables. Seeds, which are an important source of thiamin, are deficient in riboflavin.

Niacin: This is widely distributed in association with other *B* factors, especially thiamin. It is found in yeast, liver, peanuts, meat, wholemeal, potatoes and oatmeal.

Pyridoxine: Meat, liver, eggs, cereals, legumes, soya bean and yeast.

Ascorbic Acid: Fresh fruits, especially black currants, oranges, lemons and tomatoes. Other rich sources are rose hips, parsley, paprika, the outer portion of potatoes and green vegetables. The juice of grape fruit, grapes or limes is poorer in vitamin *C* than orange juice. Cow's milk contains very small amounts and prune juice almost none.

Vitamin D: Vitamin *D* has a limited distribution in ordinary foodstuffs, but can be synthesized from sterols in the skin by the action of light. It is found in fish liver oils and, to a small extent, in butter, milk and eggs.

Vitamin E: Wheat germ oil, oil from other seed embryos, green leaves, peanuts, eggs, milk and butter.

Literature.

Recent comprehensive general accounts of the vitamins will be found in the following articles: (*a*) C. A. Elvehjem: "The Water Soluble Vitamins", *The Journal of the American Medical Association*, Volume CXX, December 26, 1942, page 1388; and (*b*) H. R. Butt: "The Fat Soluble Vitamins", *The Journal of the American Medical Association*, Volume CXX, November 28, 1942, page 1030.

References.

(1) F. W. Clements: "Rickets in Infants under One Year: The Incidence in an Australian Community and a Consideration of the Ætiological Factors", THE MEDICAL JOURNAL OF AUSTRALIA, March 21, 1942, page 336.

(2) F. W. Clements: "The Symptoms of Partial Vitamin B_1 Deficiency in Breast-Fed Infants", THE MEDICAL JOURNAL OF AUSTRALIA, January 3, 1942, page 12.

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